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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,851	07/21/2006	Silvio Aime	57708/460	9446

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KRAMER LEVIN NAFTALIS & FRANKEL LLP
INTELLECTUAL PROPERTY DEPARTMENT
1177 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

EXAMINER	
RIDER, LANCE W	

ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
03/19/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

klpatent@kramerlevin.com

Office Action Summary	Application No.	Applicant(s)	
	10/552,851	AIME ET AL.	
	Examiner	Art Unit	
	LANCE RIDER	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-19 and 22-28* is/are pending in the application.

4a) Of the above claim(s) *18,19 and 22-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-17 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 October 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/11/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1-19, and 22-28 are currently pending, claims 1-9, and 20-21 have been canceled. Claims 18-19, and 22-27 have been withdrawn due to the election requirement filed on December 11th 2009.

Election/Restrictions

Applicant's election without traverse of Group I, methods of imaging using CEST based MRI, in the reply filed on January 11th 2010 is acknowledged.

Claims 18-19 and 22-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on January 11th 2010. Claim 18, drawn to a CEST agent, was inadvertently included in group I in the election requirement filed on December 11th 2009. Claim 18 has been withdrawn given applicant's election of imaging methods (Group I) rather than the imaging agents (Group II). Claim 28 is stated to be a CEST based MRI method yet has no positive active steps. Claim 28 has been included in the prosecution and treated as a method.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 28 is rejected under 35 U.S.C. 101 because the claimed recitation of a method, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 recites the term “mobile proton”. What is a mobile proton? Did applicants intend to mean the proton is capable of chemical exchange with bulk water? Does this mean the proton undergoes quantum tunneling? What conditions cause this exchange to occur and how fast? Does this mean the proton displays a particular pKa in a certain environment? Claims 11-17 depend upon this claim and do not fix the indefinite nature of this claim.

Claim 10 recites the term “bound to a paramagnetic chelate complex”. It is unclear what subject this verb is referring to. Is it the CEST agent, the substrate

molecule, the water? What exactly is bound to a paramagnetic chelate complex? Claims 11-17 depend upon this claim and do not fix the indefinite nature of this claim.

Claim 16 recites "having a ... Ka greater than 10". Does applicant intend 10 molar, 10 millimolar? The lack of any units in this claim renders it indefinite.

Claim 28 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01.

The omitted steps are: Administration of the CEST agent and performing MR imaging of the subject. Claim 28 is so vague and indefinite that it is impossible to compare it to the prior art of record. The examiner has, therefore, made no attempt to examine this claim beyond rejecting it as indefinite and as being drawn to non-statutory subject matter.

Information Disclosure Statement

The Information Disclosure Statement (IDS), filed by applicant on October 11th 2005 has been considered by the examiner in the present case.

Claim Objections

Claim 10 is objected to because of the following informalities: Claim 10 recites:

A method of imaging a subject comprising the steps of administering into a subject a paramagnetic CEST agent comprising ... substrate molecule (SH) endowed with at least one mobile proton in exchange with bulk water bound to a paramagnetic chelate complex (SR) of a metal ion selected from iron (II) (high-spin configuration), iron (III),

cobalt (II), rhodium (II), copper (II), nickel (II), cerium (III), praseodymium (III), neodymium (III), dysprosium (III), erbium (III), terbium (III), holmium (III), thulium (III), ytterbium (III) and europium (III); and imaging said subject using a CEST based MRI procedure.

The claim should include [a] at the position indicated by . . . in the claim recited above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 10-12, and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Balaban, et al., International Patent Application Publication WO 00/66180 in view of Aime, S., et al., (Magnetic Resonance in Medicine, 2002).

Balaban teaches methods for imaging subjects by administering CEST agents to the subjects and imaging them. (See claims 1-5.) Balaban teaches the use of diamagnetic CEST agents with mobile protons such as sugars, amino acids (Such as arginine), and polymers thereof. (See claims 7 and 12 of Balaban.) Arginine as a polymer (taught by Balaban) reads on polyarginine and a polyaminoacid as recited in instant claims 11 and 12. Balaban states that there are many suitable agents capable of being used in CEST, such as compounds containing functional groups bearing a proton capable of chemical exchange like amides, amines, carboxyls, hydroxyls, and sulfyhdryls. (See page 4, lines 5-7.) Balaban teaches that combinations of different contrast agents can be used in this method. (See page 14, lines 15-20.) Balaban also teaches that metals can be used to enhance the chemical shifts of protons in biomolecules and suggests these methods may be useful in CEST MRI. (See page 23, lines 25-28.) Balaban teaches administering aqueous solutions of the compounds meeting the limitation of instant claim 15. (See claim 16 of Balaban.) Balaban also teaches the use of two or more contrast agents together to determine the pH in a subject. (See page 4, paragraph 3.)

Balaban does not disclose administering both a paramagnetic CEST agent containing a lanthanide such as ytterbium or europium along with a covalently or non-covalently bound "substrate molecule".

Aime teaches using the macrocycle DOTAM-Gly bound to lanthanides such as ytterbium and europium for CEST based MRI. The ligand is paramagnetic, and has a covalently bound “substrate molecule” (glycine), meeting the limitations of instant claims 10, 15, and 17. The glycine is covalently bound to the paramagnetic macrocycle. Being covalently bound, the Ka for the glycine and the substrate is dependent upon the strength of the carbon-nitrogen bond in the compounds and is so high it is practically un-measurable, meeting the limitation of instant claim 16. Aime also discloses that this agent is useful for sensing the pH of solutions using CEST MRI.

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to use the paramagnetic pH sensitive CEST ligand DOTAM-Gly in the CEST based MRI methods of Balaban in order to form an improved method of performing CEST based MRI which could sense the pH of the tissues in the subject. Using both the polyarginine agent suggested by Balaban and the DOTAM-Gly agent taught by Aime together would have been further obvious. The skilled artisan would have been motivated to make this combination as Balaban suggests using two or more CEST agents to determine the pH in a subject, and Aime suggest DOTAM-Gly is just such a pH sensitive CEST agent.

It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be

used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) **MPEP 2144.06.**

Claims 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Balaban, et al., International Patent Application Publication WO 00/66180 and Aime, S., et al., (Magnetic Resonance in Medicine, 2002) as applied to claims 10-12 and 15-17 above, in further view Frullano, L., et al., (Topics in Current Chemistry, 2002).

Balaban and Aime disclose methods and contrast agents for performing pH sensitive CEST based MRI. Balaban also teaches almost any agent with an appropriate mobile proton can be used in CEST based MRI methods. Aime teaches using paramagnetic macrocyles having a functional group containing a mobile proton in CEST MRI methods. The skilled artisan at the time of the invention would have understood from the teachings of Balaban and Aime (Magnetic Resonance in Medicine, 2002) that the CEST MRI technique was compatible with many different molecules including paramagnetic macrocyles. Both Aime (Magnetic Resonance in Medicine, 2002) and Aime (JACS Communications, 2002) teach that many different paramagnetic macrocycles are useful in CEST MRI when they have a functional group attached containing a mobile proton.

Balaban, Aime (Magnetic Resonance in Medicine, 2002), and Aime (JACS Communications, 2002) do not teach the specific paramagnetic macrocycle $[LnDOTP]^{4-}$.

Frullano teaches the use of the paramagnetic macrocycle $[LnDOTP]^{4-}$ in MRI. Frullano teaches that this macrocycle is predominantly in the 4- state at physiological pH (pH 7.4) and that the molecule has mobile protons indicated by 4 protonation steps occurring between pH 2 and 10. Frullano also shows that this complex binds to polyarginine leading to an enhanced relaxivity of the molecule. (See page 43, paragraphs 1 and 2.) Frullano also teaches that [LnDOTP] complexes interact with positively charged patches on protein surfaces.

From the teachings of Balaban, Aime (Magnetic Resonance in Medicine, 2002), and Frullano one skilled in the art at the time of the invention would have immediately recognized $[LnDOTP]^{4-}$ as a CEST agent. Balaban teaches that CEST agents require mobile protons. Aime (Magnetic Resonance in Medicine, 2002) teaches that cyclic macrocycles with functional groups containing mobile protons work effectively in CEST MRI. Frullano teaches that $[LnDOTP]^{4-}$ has functional groups with mobile protons, was already a recognized MRI contrast agent, and shares the same core structure as the CEST agents taught by Aime (JACS Communications, 2002).

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to use the macrocycle $[LnDOTP]^{4-}$ in the methods Balaban and Aime for a number of reasons. First it would been prima facie obvious to use the combination of $[LnDOTP]^{4-}$ taught by Frullano with the polyarginine taught by Balaban in order to form a mixture of CEST agents with a higher relaxivity than either $[LnDOTP]^{4-}$ or polyarginine alone had, yielding higher contrast in the CEST based MRI images. Second it would have been prima facie obvious to use the macrocycle $[LnDOTP]^{4-}$ in

order to form an improved method of sensing the pH of tissues in the range of pH 2-10. The $[LnDOTP]^{4-}$ macrocycle shows 4 protonation steps in this range indicating that it would be suitable for measuring changes in pH in this range. The skilled artisan would have predicted that this molecule would function in CEST based MRI as Balaban required that the CEST agents had mobile protons, which $[LnDOTP]^{4-}$ was known to have, and Aime had shown that macrocyclic compounds (such as $[LnDOTP]^{4-}$) were useful in CEST based MRI methods.

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Balaban, et al., International Patent Application Publication WO 00/66180 and Aime, S., et al., (Magnetic Resonance in Medicine, 2002), and Frullano, L., et al., (Topics in Current Chemistry, 2002) as applied to claims 10-13 and 15-17 above, and further in view of Aime, S., et al., (JACS, 1995).

Balaban, Aime (Magnetic Resonance in Medicine, 2002), and Frullano teach CEST based MRI methods using polyarginine and $[LnDOTP]^{4-}$ as discussed above.

Balaban, Aime (Magnetic Resonance in Medicine, 2002), and Frullano do not teach using the contrast agents in lipisomes, microemulsions, or protein cavities.

Aime (JACS, 1995) teaches covalently or non-covalently binding the macrocycle [LnDOTP] and other lanthanide complexes into macromolecular systems such as polylysine (a positively charged protein like polyarginine), albumin, dextran, micelles, and hemoglobin. Aime also discloses including lanthanide complexes into larger slower

tumbling systems yields large relaxation enhancements for the lanthanide systems. (See page 9365, paragraph 1.)

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to combine the [LnDOTP] and polyarginine complexes taught by Balaban, Aime (Magnetic Resonance in Medicine, 2002), and Frullano into proteins or micelles as taught by Aime (JACS, 1995) in order to increase the relaxation times of the agents and provide higher contrast images in the CEST methods taught by Balaban, Aime (Magnetic Resonance in Medicine, 2002), and Frullano. The skilled artisan would have predicted that by placing [LnDOTP] and polyarginine into proteins or micelles that the relaxation times for the complexes would be enhanced given the teaching of Aime (JACS, 1995). The skilled artisan would have further predicted that this would increase the contrast provided by the agents in the CEST MRI methods as Aime (JACS, 1995) also teaches that contrast enhancement is affected by the relaxivity of paramagnetic complexes.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 10-17 and 28 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 6-8, 10, 13, 14, and 18 of copending Application No. 10/502701.

Although the conflicting claims are not identical, they are not patentably distinct from each other because: Both sets of claims are directed to a method of analyzing a subject using CEST based MRI by administering a paramagnetic chelate complex. The claims of the 10/502701 application describe CEST based MRI methods and disclose specific contrast agents to be used in those methods such as (Eu(III) DOTAM-Gly), anticipating the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are currently allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LANCE RIDER whose telephone number is (571)270-1337. The examiner can normally be reached on M-F 11-12 and 1-4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571)272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LANCE RIDER/
Examiner, Art Unit 1618

/Eric E Silverman/
Primary Examiner, Art Unit 1618